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OFFICE OF  
PREVENTION, PESTICIDES AND  
TOXIC SUBSTANCES

TXR NO. 0050515

DATE: March 1, 2002

MEMORANDUM

SUBJECT: IPROVALICARB - Report of the Hazard Identification Assessment Review Committee.

FROM: Alan C. Levy, Toxicologist  
Registration Action Branch 2  
Health Effects Division (7509C)

Handwritten signature of Alan C. Levy.

THRU: Jess Rowland, Co-Chair  
and  
Elizabeth Doyle, Co-Chair  
Hazard Identification Assessment Review Committee  
Health Effects Division (7509C)

Handwritten signature of Jess Rowland.

Handwritten signature of Elizabeth Doyle.

TO: William Cutchin, Risk Assessor  
Science Information Management Branch  
Health Effects Division (7509C)

PC Code: 098359

On January 31, 2002, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for iprovalicarb with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for acute and chronic risk assessments. The potential for increased susceptibility of infants and children from exposure to iprovalicarb was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996. The conclusions drawn at this meeting are presented in this report.

### Committee Members in Attendance

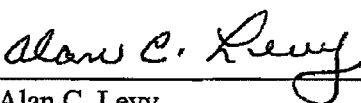
Members present were: Ayaad Assaad, William Burnam, Jonathan Chen, Paula Deschamp, Elizabeth Doyle, Pamela Hurley, John Liccione, Elizabeth Mendez, David Nixon, Jess Rowland and Virginia Fornillo.

Members(s) in absentia were: none

Also in attendance were: Edwin Budd and Alan Levy

Data evaluation prepared by: Alan C. Levy, Registration Action Branch 2.

Data Evaluation/Report Presentation:

  
\_\_\_\_\_  
Alan C. Levy  
Toxicologist

## 1. INTRODUCTION

Iprovalicarb (also known as TM-210, SZX 0722 and MELODY) is a new systemic fungicide active ingredient that is proposed for use in the European Union to prevent and control downy mildew in/on grapes. MELODY WG 50 is a fungicide based on iprovalicarb and belongs to a new chemical class which is derived from natural amino acids. It acts by contact and has systemic properties. MELODY WG 50 has preventive properties, and exhibits curative and eradication action against Oomycete fungi, particularly downy mildews. Regarding application of MELODY WG 50 on grapes for downy mildew (water dispersible granules), 0.24-0.60 kg/ha (hectre) equivalent to 0.214-0.534 lb/acres, is applied a maximum of five (5) times/season (maximum of 2 applications prior to flowering, 3 post-flowering), at intervals of 10-14 days with a pre-harvest interval (PHI) of 28 days.

To support the proposed use of iprovalicarb on grapes in Europe, a tolerance petition for iprovalicarb residues in/on imported grapes and raisins is presented. MELODY WG 50 is proposed for registration in France for use on grapes. Formulations containing iprovalicarb in combination with other active ingredients are proposed for registration in other European countries for use on grapes. The proposed imported commodity of greatest interest is wine.

On January 31, 2002, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for iprovalicarb with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for acute and chronic risk assessments. The potential for increased susceptibility of infants and children from exposure to iprovalicarb was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996.

The DERs, Reference Doses, Endpoints and NOAELs/LOAELs are to be considered usable ONLY for this action (import tolerance on grapes and raisins) and are not to be used for any other action. Should other petitions be submitted, a reevaluation by HED will need to be made regarding the acceptance of DERs for the determination of endpoints.

## 2. HAZARD IDENTIFICATION

### 2.1 Acute Reference Dose (RfD)

An appropriate endpoint attributable to a single dose was not identified in the database, including the rat and rabbit developmental studies where no toxicity was seen at the limit dose. An acute RfD is not established.

## 2.2 Chronic Reference Dose (RfD)

Study Selected: One-year feeding study in dogs

Guideline # 870.4100

MRID No.: 44865721

**EXECUTIVE SUMMARY:** In a 1-year dog study (MRID not available), SZX 0722 technical (98.7 %) was administered to beagle dogs (4/sex/group), in the diet at doses of 0, 80, 800, or 8000 ppm (0, 2.62/2.68, 24.69/28.10, 256.21/261.70 mg/kg bw/day, males/females), for 53 weeks. There were no treatment related clinical signs of toxicity. At 8000 ppm, incomplete food uptake was observed in one animal of each sex, and body weight gain was reduced in males. A slight increase in poikilocytosis occurred in females at 800 and above, and in males at 8000 ppm, and there was a marginal increase in the number of normoblasts in females at 8000 ppm. Serum liver enzyme activities (ALT and ALP) were increased at  $\geq 800$  ppm in both sexes, while AST, GLDH and GGT activities were increased in both sexes at 8000 ppm. Plasma albumin was decreased at 8000 ppm in both sexes. One male at 8000 ppm, had decreased plasma cholesterol and T4 levels, and increased total bilirubin, which were attributed to marked liver injury and severe emaciation. At necropsy, one female at 800 ppm and one male at 8000 ppm, were judged to be skinny. At  $\geq 800$  ppm, there were increases in the relative and absolute liver weights in both sexes, as well as swelling, enlargement, distinct lobulation and discolouration of the liver, which correlated with histopathological changes. Microscopically, there was hypertrophy, fatty change and increased intracellular iron storage in livers of both sexes at 800 ppm and above, and focal hepatic necrosis, single cell necrosis, multi lamellar inclusions, and binucleated hepatocytes at 8000 ppm. Two males, and one female at 8000 ppm had liver fibrosis, which in one animal was accompanied by marked nodular hyperplasia. The gall bladders of animals of both sexes contained large quantities of adhesive mucous at 800 ppm and above, and at 8000 ppm, there was pseudo gland formation, and increased lymphoid tissue in the gall bladder walls. Two males at 8000 ppm had inactive prostate glands, and one of these animals showed decreased spermatogenesis in the testes. Liver triglyceride content was increased at 800 ppm and above, which may be indirectly attributable to other toxic events occurring in the liver at these dose levels. There was a dose-dependant increase in the levels of liver microsomal enzymes; N-demethylase, O-demethylase and cytochrome P-450-content, at 80 ppm and above in both sexes. The microsomal enzyme induction was considered an adaptive response rather than an adverse effect. **The LOAEL in dogs was 800 ppm (24.69 and 28.10 mg/kg bw/day in males and females, respectively), based on the biochemical and morphological liver effects (e.g. swelling, enlargement, distinct lobulation and discolouration, increases in absolute and relative liver weights, and activities of ALT and ALP, hepatocellular hypertrophy and periportal fatty change) at this dose. The NOAEL was 80 ppm (2.62 and 2.68 mg/kg bw/day in males and females, respectively).**

This study in dogs is acceptable and satisfies the guideline requirement for a 1-year oral toxicity study in dogs (OPPTS 870.4100; OECD 452).

**COMPLIANCE:** Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

Dose and Endpoint for Establishing RfD: NOAEL of 2.62 mg/kg/day based on biochemical and morphological liver effects (swelling, enlargement, distinct lobulation and discoloration, increases in absolute and relative liver weights, increases in ALT and ALP activities and hepatocellular hypertrophy as well as periportal fatty change) at 24.69 mg/kg/day (LOAEL).

Uncertainty Factor(s): 100, based on 10 for intraspecies variation and 10 for interspecies extrapolation.

$$\text{Chronic RfD} = \frac{2.62 \text{ mg/kg/day (NOAEL)}}{100 \text{ (UF)}} = 0.0262 \text{ mg/kg/day}$$

Comments about Study/Endpoint/Uncertainty Factor(s): The dose selected is supported by the subchronic studies presented below.

1. 90-Day Dietary (MRID 44865714): Doses were 0, 9.1, 62.5 or 1250 mg/kg/day for both sexes. The NOAEL was 9.1 mg/kg/day. The LOAEL was 62.5 mg/kg/day based on increased absolute and relative liver weight, hepatocellular hypertrophy, increased serum activity of alkaline phosphatase and decreased plasma protein levels.

2. 28-Day Dietary (MRID 44865712): Doses were (mg/kg/day) for males = 0, 3.0, 31.5, 280 or 1322; for females = 0, 3.4, 35.0, 169.5 or 1164.5. The NOAEL was 3.0 mg/kg/day for males and 3.4 mg/kg/day for females. The LOAEL was 31.5 mg/kg/day for males and 35.0 mg/kg/day for females based on hepatocellular hypertrophy, vacuolated hepatocytes and increased alkaline phosphatase.

3. 28-Day Dietary + 28-Day Recovery (MRID 44865713): Doses were 0, 0.41, 0.77, 1.61, 2.93-3.01 or 0 + 2.93-3.01 recovery for both sexes. The systemic NOAEL was 2.93-3.01 mg/kg/day (the highest dose tested). Liver microsomal enzymes were determined (N-Demethylase, O-Demethylase and Cytochrome P-450): The LOAEL for N-Demethylase was (mg/kg/day) 1.61, for Cytochrome P-450 was 1.61 and O-Demethylase was 3.01. After 28 days of recovery, all microsomal enzymes were normal. Levels of AST, ALT and ALK levels of treated dogs did not differ from controls during either treatment or recovery.

In addition, similar liver effects (increased weights and/or hepatocellular hypertrophy and/or increased enzyme activity) were reported (at doses at or higher than 263 mg/kg/day) in the following rat studies: 2-year dietary toxicity/carcinogenicity study (MRID 44865723), 2-generation dietary reproduction study (MRID 44835720), 90-day dietary study (MRID 44865710) and 28-day dietary study (MRID 44865709).

### **2.3 Occupational/Residential Exposure**

Since this action is for an import tolerance, occupational and residential exposure risk assessments are not required. The dose endpoints were not selected.

## **3. CLASSIFICATION OF CARCINOGENIC POTENTIAL**

Because PMRA of the Canadian government considered Iprovalicarb to be carcinogenic in rats and assigned a Q<sub>1</sub>\*, HED made the decision to take this chemical to the Cancer Assessment Review Committee (CARC) for evaluation.

### **3.1 Two-Year Dietary Toxicity/Carcinogenicity Study in Rats - MRID No. 44865723**

**EXECUTIVE SUMMARY:** In a combined chronic/carcinogenicity study (MRID not available), SZX 0722 (95.8% - 98.5%) was administered to 50 rats (Bor: WISW[SPF-Cpb)/sex/dose in the diet (admixed with 1% peanut oil), at concentrations of 0, 500, 5000, and 20000 ppm (0, 26.0, 262.5, or 1109.6 and 0, 31.7, 326.3, and 1379.7 mg mg/kg bw/day in males and females respectively) for 24 months. Ten additional rats/sex/dose were treated similarly and included in the study for the 12 months interim sacrifice.

There were no treatment related mortalities in either sex. At 20000 ppm there was an increase in the incidence of vaginal bleeding among females, and the males had an increase in the incidence of cataracts, and turbidity of the vitreous body after one year of treatment. Treatment related decreases in body weight gain occurred in females at 20000 ppm. Plasma cholesterol levels were increased in females at 5000 ppm and above, and alkaline phosphatase activity was significantly increased in males at 20000 ppm. At interim sacrifice, the relative liver weight (compared to body mass) of females at 20000 ppm was increased (22%), and some females at 5000 ppm (2/10) and at 20000 ppm (3/10) had slight hypertrophy of hepatocytes. At study termination, there were increases in relative liver weights of females at 5000 (9%) and 20000 ppm (19%), and increased absolute liver weights of males at 20000 ppm (22%). There was also increased incidence of hepatocellular hypertrophy in females, and bile duct hyperplasia affecting both sexes at 5000 ppm and above. Furthermore, females had slightly increased incidence of thyroid follicular cell adenomas and thyroid follicular cell carcinoma at 5000 and above, with a positive trend evident for follicular adenomas. Benign transitional cell papillomas of the urinary bladder occurred in females at 20000 ppm (4%), and mixed Muellierian tumours of the uterus occurred at 5000 ppm (2%) and at 20000 ppm (4%). The increased incidence of these tumours was considered treatment related as it exceeded historical control range, or showed a positive trend. In addition, females at 20000 ppm had a slight increase in the incidence of uterine adenocarcinomas (6/50; 12%) compared to 4% (2/50) in the control group, and clitoral gland carcinomas were observed in 4% of females (2/50).

at that dose, compared to 0% in the control group. Although both these tumour types were within the historical control incidence, they may add to the number of tumours involving the uterus (Muellerian tumours) to achieve statistical and toxicological significance. In males at 20000 ppm, osteosarcomas occurred in three animals (two in the femur, one in the lower jaw) and chondrosarcoma of the nasal cavity was observed in one animal. These tumours (chondrosarcoma and osteosarcomas) were considered treatment related as both were unusual in the rat strain and outside the historical control range for the conducting laboratory.

The LOAEL in females was 5000 ppm (326.3 mg/kg bw/day), based on increases in plasma cholesterol levels, relative liver weights, hepatocellular hypertrophy and bile duct hyperplasia, as well occurrence of uterine Muellerian tumour and a positive trend for thyroid adenomas at that dose. The NOAEL in females was 500 ppm (31.7 mg/kg bw/day).

The LOAEL in males was 5000 ppm (262.5 mg/kg bw/day), based on histopathological changes in the liver (bile duct hyperplasia) at that dose and above. The NOAEL in males was 500 ppm (26.0 mg/kg bw/d).

The NOAEL for carcinogenic effects was 500 ppm, (26.0 mg/kg bw/d).

Dosing was considered adequate. It exceeded the limit dose and there were observations at the highest dose of clinical signs, organ and body weight, clinical chemistry, and histological changes in the liver, as well as a slight increase in the incidence of neoplasms in a variety of tissues (bones, thyroid, urinary bladder, and uterus).

This chronic/carcinogenicity study in the rat is acceptable, and satisfies the guideline requirement for a carcinogenicity study (83-2); OECD 453 in the rat.

**COMPLIANCE:** Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

### **3.2 Two-Year Dietary Carcinogenicity Study in Mice - MRID No. 44865722**

**EXECUTIVE SUMMARY:** In a carcinogenicity study (MRID not available), SZX 0722 technical (95.8 - 98.5 %) was administered to groups of 50 male and 50 female B6C3F<sub>1</sub> mice, in the diet at concentrations of 0, 280, 1400, and 7000 ppm (equal to 0, 58.5, 283.4, and 1566.8 mg/kg bw/day for males and 0, 97.4, 503.1, and 2544.0 mg/kg bw/day for females) for up to 105 weeks. An additional 10 animals/sex/dose were similarly treated to serve as interim sacrifices at 52 weeks. There were no treatment related effects on clinical signs, mortality, body weight, absolute food consumption and water intake. However, relative to body weight gain, food and water intakes of males at 7000 ppm were marginally (5-9%) increased. Absolute body weights of males at 7000 ppm were slightly lower (4.1%) compared to controls, throughout the study. Blood urea



concentrations were increased in both sexes at 1400 and 7000 ppm, suggestive of restricted kidney function at these dose levels. Triglyceride concentration was significantly higher in males at 7000 ppm at 52 weeks, but not at the end of the treatment period. At the interim and the final necropsy, male mice at 1400 and 7000 ppm showed lower absolute and relative kidney weights compared to controls. Both absolute and relative liver weights were increased in males at 280 ppm and above, but the increase was not dose-related. The increased absolute and relative liver weights in males at 280 ppm were attributed to the higher incidence of hepatocellular neoplasms at this dose, and not considered treatment-related, because of the lack of a dose relationship. The increase in liver weights in both sexes at 7000 ppm, was accompanied by histological changes in the tissue and considered toxicologically significant. Increases in the incidences of fatty changes in the liver were observed in male and female mice at 7000 ppm, and were considered treatment-related. At terminal necropsy, the incidence of tubular vacuolization of the kidney was markedly decreased in males at 1400 ppm and above. As the kidney histological changes correlated with decreased kidney weights and increased blood urea concentration at these dose levels, they were deemed to indicate an impairment of kidney function. There was no evidence of treatment-related tumours in either sex at all dose levels.

The LOAEL in both sexes was 1400 ppm (283.4 mg/kg bw/d in males and 503.1 mg/kg bw/d in females), based on increased blood urea concentrations (both sexes) and decreased kidney weights (males), as well as histological kidney changes in males 1400 ppm and above. The NOAEL in both sexes was 280 ppm (58.5 mg/kg bw/day).

SZX 0722 technical was not carcinogenic in mice under the conditions of this study.

This carcinogenicity study in the mouse is acceptable, and satisfies the guideline requirements for a carcinogenicity study (83-2); OECD 451 in mice.

**COMPLIANCE:** Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided. Animals scheduled for interim necropsy after one year were included in the study (but not examined histopathologically), and supplementary haematological and clinicochemical tests were conducted to detect possible chronic toxicological effects. Those deviations do not alter the acceptability of this study.

#### 4. **MUTAGENICITY**

Technical grade Iprovalicarb did not demonstrate mutagenic potential in the five studies submitted by the registrant. In addition, there was one reverse gene mutation study with the metabolite methyl-phenethylamine and one with <sup>32</sup>P-postlabelling to investigate possible DNA adduct formation in the uterus, urinary bladder epithelium and whole urinary bladder.

##### Mutagenicity Studies on Technical Grade Iprovalicarb

#### 4.1 Reverse gene mutation assay (*Salmonella typhimurium* plate test)

MRID No. 44865724

Guideline No.: 870.5100

**EXECUTIVE SUMMARY:** In a reverse gene mutation assay in bacteria, *Salmonella typhimurium* strains (TA 98, TA 100, TA 1535 and TA 1537) were exposed to SZX 0722 (iprovalicarb, purity: 98.1%) in dimethyl sulfoxide (DMSO) at concentrations of 0, 8, 40, 200, 1,000 or 5,000 µg/plate in the presence and absence of S9 mammalian metabolic activation using the standard plate method. In an independent confirmatory trial the concentrations were 0, 125, 250, 500, 1,000, 2,000 or 4,000 µg/plate in the presence and absence of S9 mammalian metabolic activation. The S9 fraction was derived from Aroclor 1254-induced rat livers.

The test substance was tested up to the highest concentration recommended for microbial assays (5,000 µg/plate), although the test substance started to precipitate at 4,000 µg/plate such that evaluation was not possible at 5,000 µg/plate. A weak strain-specific (TA100) bacteriotoxic effect was possibly observed at doses of 4,000 µg/plate and above. Evaluation of individual dose groups with respect to relevant assessment parameters (dose effect and reproducibility) indicate that the test substance did not induce a mutagenic response in the two independently performed trials. The positive controls induced the appropriate responses in the corresponding strains. **There was no evidence of induced mutant colonies over background.**

This study is classified as acceptable / guideline and satisfies the requirement for FIFRA Test Guideline 84-2; OECD 471 / 472 for *in vitro* mutagenicity (bacterial reverse gene mutation) data.

**COMPLIANCE:** Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

#### 4.2 *In vitro* Chinese hamster lung fibroblast

MRID No. 44865727

Guideline No. 870.5375

**EXECUTIVE SUMMARY:** In a mammalian cell gene mutation assay at the poxanthine-guanine-phosphoribosyl transferase locus, V79 cells (Chinese hamster lung fibroblasts) cultured *in vitro* were exposed to SZX 0722 (iprovalicarb; purity: 98.1%) at concentrations of 0, 12.5, 25, 50, 75, 100 or 125 µg/mL in the presence S9 metabolic activation and at concentrations of 0, 7.8, 15.6, 31.3, 62.5, 125 or 250 µg/mL in the absence of S9 metabolic activation.

SZX 0722 (iprovalicarb) was tested up to its limit of solubility under culture conditions. No treatment-related effect on cloning efficiency or relative population growth was observed in either the presence or absence of S9 metabolic activation. The test substance

did not induce a significant, dose-related, reproducible increase in mutation frequency compared to the solvent controls in the presence or absence of S9 metabolic activation. The positive controls, ethyl methanesulfonate (without S9 mix) and dimethylbenzanthracene (with S9 mix), induced the appropriate responses. **There was no evidence of induced mutant colonies over background; therefore, under the conditions of this *in vitro* mammalian cell gene mutation assay, SZX 0722 (iprovalicarb) was considered to be non-mutagenic.**

This study is classified as acceptable / guideline. This study satisfies the requirement for Test Guideline OPPTS 870.5300, OECD 476 for *in vitro* mutagenicity (mammalian forward gene mutation) data.

#### **4.3 Cytogenetics assay (chromosomal aberrations in Chinese hamster ovary cells)**

MRID No. 44865726

Guideline No. 870.5375

**EXECUTIVE SUMMARY:** In a mammalian cell cytogenetics assay (Chromosomal aberration), Chinese Hamster Ovary (CHO) cultures were exposed to SZX 0722 (iprovalicarb; purity - 98.7%) in ethanol at concentrations of 0, 6, 30 or 150 µg/mL in both the presence and absence of S9 mammalian metabolic activation (S9 fraction derived from Aroclor 1254-induced rat livers). The positive controls were mitomycin C (without S9 metabolic activation; final concentration - 1.0 µg/mL) and cyclophosphamide (with S9 metabolic activation; final concentration - 10 µg/mL).

The highest dose tested, 150 µg/mL, was based on the insolubility of the stock concentration at higher doses in the treatment medium. In the presence of S9 metabolic activation no cytotoxicity was observed. In the absence of S9 metabolic activation cytotoxicity was observed at 150 µg/mL at the 24 hour harvest time. When compared to controls, there were no biologically relevant or statistically significant increases in the number of metaphases with aberrations at any dose level at the 8, 24 or 30 hour harvest time in either the presence or absence of S9 metabolic activation. Positive controls induced the appropriate response. **Under the conditions of this study, there was no evidence of chromosomal aberrations induced over background.**

This study is classified as acceptable / guideline. This study satisfies the requirement for Test Guideline: *In vitro* mammalian cytogenetics [chromosomal aberration] OPPTS 870.5375; OECD 473 for *in vitro* cytogenetic mutagenicity data.

**COMPLIANCE:** Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

#### 4.4 Mouse bone marrow micronucleus assay

MRID No. 44865728

Guideline No.: 870.5375

**EXECUTIVE SUMMARY:** In a HsDd/Win:NMRI mouse bone marrow micronucleus assay, 5 animals/sex/dose/ sampling time were treated, by intraperitoneal injection (single dose), with SZX 0722 (iprovalicarb; purity - 96.7%) at doses of 0 or 2,000 mg/kg bw. Bone marrow cells, isolated from the femur, were harvested at 16, 24 and 48 hours post-treatment. The vehicle and negative control was 0.5% aqueous Cremophor emulsion (20 mL/kg bw). The positive control was cyclophosphamide (20 mg/kg bw). The treated animals exhibited the following treatment-related symptoms until sacrifice: apathy, roughened fur, spasm, difficulty in breathing and diarrhea. Their feeding behaviour appeared normal and there were no mortalities. The ratio of normochromatic erythrocytes (NCE) per 1,000 polychromatic erythrocytes (PCE) was increased in the treated group over time. This was statistically significant at 48 hours. There was no biologically relevant or statistically significant difference between the negative control group and the treated group with respect to the incidence of micronucleated polychromatic erythrocytes or micronucleated normochromatic erythrocytes at any sacrifice time for both sexes. SZX 0722 was tested at an adequate dose based on the maximum tolerated dose (MTD) as indicated in OECD Guideline 474 or based on the limit dose (2,000 mg/kg bw) as indicated in OPPTS 870.5395 [§84-2]. The positive control, cyclophosphamide (20 mg/kg bw), induced the appropriate response. **There was not a significant increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow after any treatment time.**

This study is classified as acceptable / guideline. This study satisfies the requirement for Test Guideline OPPTS 870.5395; OECD 474 for *in vivo* cytogenetic mutagenicity data.

**COMPLIANCE:** Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

#### 4.5 Unscheduled DNA synthesis, primary rat hepatocyte cultures

MRID No. 44865729

Guideline No.: 870.5375

**EXECUTIVE SUMMARY:** In an unscheduled DNA synthesis assay, primary rat hepatocyte cultures were exposed to SZX 0722 (iprovalicarb; purity: 98.7%) in dimethylsulfoxide (DMSO; final concentration  $\leq 1\%$  v/v) at concentrations of 0, 50, 150, 200, 250, 300, 400 or 500  $\mu\text{g/mL}$  for 16-24 hours. The positive control substance was 2-acetylaminofluorene in DMSO (2-AAF; final concentration - 0.25 and 0.50  $\mu\text{g/mL}$ ). SZX 0722 was tested up to cytotoxic (250 and 300  $\mu\text{g/mL}$ ) and precipitating concentrations (400 and 500  $\mu\text{g/mL}$ ). The initial trial was considered invalid since the mean nuclear net grain value of the vehicle control was outside the range of the historical control data and the positive control (0.25  $\mu\text{g/mL}$  2-AAF) did not induce an effect which

was strong enough according to acceptable assay criteria. In the second trial hepatocyte viability was 84.7 and 75.8% after isolation and attachment, respectively, demonstrating that the hepatocyte cultures were in good condition for the UDS assay. Precipitation of the test substance was observed at 400 and 500 µg/mL. The test substance exhibited clear cytotoxic effects at 250 and 300 µg/mL (19.3 and 52.6% relative survival, respectively) and probable cytotoxic effects at 200 µg/mL (71.4% relative survival). There were no biologically relevant or statistically significant differences in nuclear labelling or in the percentage of cells in repair between the treatment groups and the vehicle control. The positive control (0.5 µg/mL 2-AAF) induced the appropriate response. **There was no evidence that unscheduled DNA synthesis, as determined by radioactive tracer procedures [nuclear silver grain counts] was induced.**

This study is classified as acceptable / guideline. This study satisfies the requirement for Test Guideline OPPTS 870.5550; OECD 482 for other genotoxic mutagenicity data.

**COMPLIANCE:** Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

#### Mutagenicity Study on the Metabolite of Iprovalicarb

#### **4.6 Reverse gene mutation assay (*Salmonella typhimurium* plate test)**

MRID No. 44865725

Guideline No.: 870.5100

**EXECUTIVE SUMMARY:** In a reverse gene mutation assay in bacteria, histidine-auxotrophic strains of *Salmonella typhimurium* (TA 1535, TA 100, TA 1537, TA 98 and TA 102) were exposed to P-Methyl-phenethylamine (98.8%) dissolved in DMSO, at concentrations of 0, 16, 50, 158, 500, 1581 or 5,000 µg/plate, in the presence and absence of S9 mammalian metabolic activation using the standard plate method, in two independent trials. The S9 fraction was derived from Aroclor 1254-induced rat livers. The test substance was tested up to the highest concentration recommended for microbial assays (5,000 µg/plate). Doses greater than 50 µg/plate caused some strain specific cytotoxic effects. Evaluation of individual dose groups with respect to relevant assessment parameters indicate that the test substance did not induce a mutagenic response (biologically relevant increase in mutant counts, in comparison to controls) in the two trials. There was no evidence of induced mutant colonies above background. The positive controls (sodium azide, nitrofurantoin, 4-nitrophenylene diamine, cumene hydroperoxide, and 2-amino-anthracene) induced the appropriate responses in the corresponding strains. **Therefore, P-Methyl-phenethylamine was non-mutagenic in the Ames assay, using *Salmonella typhimurium* strains, in the presence and absence of S-9 metabolic activation.**

This study is classified as acceptable / guideline and satisfies the requirement for FIFRA Test Guideline 84-2; OECD 471 / 472 for *in vitro* mutagenicity (bacterial reverse gene mutation) data.

**COMPLIANCE:** Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

<sup>32</sup>-Postlabelling to Investigate Possible DNA Adduct Formation

**4.7 In vivo <sup>32</sup>P-postlabelling assay, possible DNA adduct formation (uterus, urinary bladder epithelium and whole urinary bladder).**

MRID No. 44865730

Guideline No.: none

**EXECUTIVE SUMMARY:** The <sup>32</sup>P-postlabelling assay was employed to investigate SZX 0722 (iprovalicarb; purity 96.4%) *in vivo* in female Wistar rats for possible DNA adduct formation in the uterus, urinary bladder epithelium and whole urinary bladder. The test substance was administered to 9 female rats/dose in the diet (*ad libitum*) at dose levels of 0, 10,000 or 20,000 ppm for 7 days. Approximately 17 hours prior to sacrifice, the positive control animals (4 animals/group) received a single dose of 2-acetylaminofluorene (2-AAF; final concentration = 120 mg/kg bw) or 7,12-dimethylbenzanthracene (DMBA; final concentration = 150 mg/kg bw) by oral gavage.

There were no treatment-related effects on mortality, clinical signs, food consumption or water consumption. Body weight development was retarded at 10,000 and 20,000 ppm. Based on the data presented in the study report, no SZX 0722-induced DNA adducts could be detected in the uterus, urinary bladder epithelium or in the whole urinary bladder. The positive control substance, DMBA, induced the appropriate response (DNA adducts) in the uterus, urinary bladder and in the whole urinary bladder. In the urinary bladder epithelium 2-AAF induced the appropriate response only after butanol extraction. After nuclease P1 enrichment no DNA adducts could be detected. The study author concluded that the lack of effect was not due to the inappropriateness of the test performance but due to the fact that nuclease P1 enrichment is not suitable for the detection of 2-AAF specific adducts in urinary bladder epithelium. **Based on the study findings, SZX 0722 was assessed as negative in the <sup>32</sup>P-postlabelling assay *in vivo* in uterus, urinary bladder epithelium and whole urinary bladder.**

**Study Deficiencies:** Currently, there are no DACO requirements and no accepted guidelines available for the <sup>32</sup>P-post-labelling *in vivo* assay. This study was a non-guideline study to assess whether SZX 0722, or its metabolites, are able to form DNA adducts in the female rat uterus and urinary bladder epithelium *in vivo* after application in the diet for 7 days. Measurement of covalently formed DNA adducts is considered to be a tool to assess the ability of a chemical to reach and alter the DNA. Stable DNA adducts can be detected by the <sup>32</sup>P-postlabelling method by incorporation of <sup>32</sup>P into non-

radioactive nuclei acid constituents by enzyme-catalysed derivatization followed by a chromatographic separation of radioactive products. The <sup>32</sup>P-postlabelling assay is considered to be particularly valuable in assessing genotoxicity and the carcinogenicity potential of chemicals and their metabolites. The methods used in this study were considered to represent further developments of the techniques originally described by Randerath et al (1981; Proc. Natl. Acad. Sci. USA., 78, 6126-6129), Reddy and Randerath (1986; Carcinogenesis, 7, 1543-1551) and Gallagher et al (1989; Cancer Letters, 45, 7-12). This study appears to be acceptable for the purpose for which it was intended. However, this study is not a required guideline study and in the absence of any accepted guidelines the reviewer cannot attest to the significance of the study author's conclusions or to the validity of the study. This study should not impact on the determination of the genotoxicity potential of SZX 0722 since it is not a required guideline study and the genotoxicity potential of SZX 0722 has been adequately addressed in DACO's 4.5.4, 4.5.5, 4.5.6, 4.5.7 and 4.5.8.

**COMPLIANCE:** Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

## 5. **FQPA CONSIDERATIONS**

### 5.1 **Adequacy of the Data Base**

The available toxicology data base for Iprovalicarb includes the following acceptable studies:

1. Developmental toxicity study, rats	OPPTS 870.3700, MRID 44865716
2. Developmental toxicity study, rabbits	OPPTS 870.3700, MRID 44865718
3. 2-Generation reproduction study, rats	OPPTS 870.3800, MRID 44865720
4. Acute neurotoxicity study, rats	OPPTS 870.6200, MRID 44865731
5. Subchronic neurotoxicity study, rats	OPPTS 870.6200, MRID 44865732

The following guideline studies are not available:

1. Acute delayed neurotoxicity study, hens	OPPTS 870.6100
2. Developmental neurotoxicity study, rats	OPPTS 870.6300

### 5.2 **Neurotoxicity Data**

In the acute neurotoxicity study in rats (MRID No. 44865731), doses of 0, 200, 800 or 2000 mg/kg were administered as a single gavage dose, followed by 14 days of observation. There were no systemic or neurotoxic effects reported at any doses.

In the subchronic neurotoxicity study (13 weeks by dietary admix) in rats (MRID No. 44865732), doses were 0, 1250, 5000 or 20000 ppm (mg/kg/day: males = 0, 86, 342 or 1434; females = 0, 131, 476 or 2314). The systemic NOAEL was 86 mg/kg/day for males and 476 mg/kg/day for females. The systemic LOAEL was 342 mg/kg/day for males based on decreased body weight and 2314 mg/kg/day for females based on decreased body weight and increased food consumption. The neurotoxicity NOAEL was the highest dose tested in both males and females. There were no signs of neurotoxicity in any of the other studies reviewed (subchronic, chronic, developmental or reproduction).

### **5.3 Developmental Toxicity**

#### **5.3.1 Executive Summary for Developmental Toxicity Study in Rats** [OPPTS 870.3700, MRID 44865716]

In a developmental toxicity study (MRID not available) SZX 0722 (95.8 % a.i.) was administered by gavage to inseminated Wistar (Hsd/Cpb:WU) rats, 28-29/dose, at dose levels of 0, 100, 300, and 1000 mg/kg bw/day, from gestation day-6 through day-15. The animals were observed daily for clinical signs and mortality. Fetuses were delivered by caesarian section on the 20th day of gestation and the dams were subjected to gross pathological evaluation. All fetuses were assessed for external gross anomalies. One half of the fetuses was examined for visceral anomalies and the other half was processed and evaluated for skeletal abnormalities. There were no treatment related clinical signs, mortalities nor effects on body weight or food consumption, throughout the gestation period, at all dose levels. There were no treatment-related effects on developmental parameters; including incidences of malformations, skeletal deviations (delayed ossification or variation) or on general reproductive parameters (gestation rate, number of dams with viable fetuses, number of corpora lutea, placental weight, embryo-fetal resorption rates, number and sex ratio of live fetuses), up to the highest dose tested 1000 mg/kg bw.

**The LOAEL for both maternal and developmental toxicity in the rat was > 1000 mg/kg bw, based on the absence of treatment related toxicity in the dams or in the fetuses at the highest dose tested (1000 mg /kg bw/day). The NOAEL for maternal and developmental toxicity was 1000 mg /kg bw/day. Under conditions of this study, SZX 0722 did not show developmental toxicity in rats.**

The developmental toxicity study in the rat is classified as acceptable and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; §83-3; OECD 414) in rats.

**COMPLIANCE:** Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.



### **5.3.2 Executive Summary for Developmental Toxicity Study in Rabbits**

[OPPTS 870.3700, MRID 44865718]

In a developmental toxicity study (MRID not available), SXZ 0722 ( 95.8 % a.i), in 0.5 % Tylose suspension) was administered daily to 16 mated female Russian rabbits (16/dose), by gavage, at dose levels of 0, 100, 300, or 1000 mg/kg bw/day from day-6 through day-16 of gestation. There was no treatment-related maternal systemic toxicity nor reproductive/developmental toxicity. **The maternal LOAEL was > 1000 mg/kg bw/day, based on absence of treatment related toxicity at the highest dose tested. The maternal NOAEL was 1000 mg/kg bw/day. There were no treatment-related effects in developmental parameters. The developmental LOAEL was > 1000 mg/kg bw/day, based on absence of treatment related developmental toxicity at the highest dose. The developmental NOAEL is 1000 mg/kg bw/day. Under conditions of this study, SXZ 0722 did not show teratogenic effects in rabbits up to the dose level of 1000 mg/kg bw/day.**

The developmental toxicity study in the rabbit is classified acceptable, and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; §83-3; OECD 414) in rabbits.

**COMPLIANCE:** Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

### **5.4 Reproductive Toxicity**

#### **5.4.1 Executive Summary for 2-Generation Reproduction Study in Rats**

[OPPTS 870.3800, MRID 44865720]

In a 2-generation reproduction study (MRID not available)], SZX 0722 (99.2%) was administered to 28-30 Wistar (ICO:WU (IOPS Cpb) rats/sex/dose in the diet, at dose levels of 0, 100, 2000 or 20000 (equal to pre-mating doses: 0, 7.3, 146.3 or 1514.3 mg/kg bw/day in males and 0, 9.6, 190.4 or 2074.0 mg/kg bw/day in females of F<sub>0</sub> generation and 0, 7.7, 155.3, 1838.0 mg/kg bw/day in males or 0, 10.8, 239.5, 2944.1 mg/kg bw/day in females of F<sub>1</sub> generation), over 2 generations with one litter per generation [mean 0, 7.5, 150.8, 1676.2 or 0, 10.1, 214.95, 2509.1 mg/kg bw/day in males and females respectively].

There were no treatment-related clinical signs, or mortality in F<sub>0</sub> or F<sub>1</sub> parental animals of either sex at all dose levels. At 20000 ppm, parental F<sub>0</sub> and F<sub>1</sub> females consumed more feed (14.7% and 23% respectively) than the controls during the pre-mating period, and F<sub>1</sub> males had significantly decreased (10%) terminal body weight. In addition, at 20000 ppm, F<sub>1</sub> male and female parents had significantly increased relative liver weights (11.4% and 28.3%, respectively) compared to controls. There was also a treatment-related increase in the incidence of bile duct proliferation in F<sub>1</sub> parental males at 20000

ppm. There were no treatment-related effects on reproductive parameters in F<sub>0</sub> and F<sub>1</sub> parental animals of both sexes (sperm parameters in males and estrus cycles, pre or post-implantation losses in females), at all dose levels.

Among the offspring, there were no treatment-related effects on the number of pups born, live birth index, pups sex ratio, mean litter size at birth in F<sub>1</sub> or in F<sub>2</sub> pups at all dose levels. At 20000 ppm, slightly reduced litter weights were observed at weaning in both generations, and were considered toxicologically significant. In addition, F<sub>1</sub> pups at 20000 ppm group, had a significantly lower mean lactation index than the controls. Among F<sub>2</sub> pups, there was no treatment related change in the lactation indices at all dose levels. There were no treatment-related malformations, skeletal deviations, maturation of external sexual organs, or gross pathological findings in any of the F<sub>1</sub> or F<sub>2</sub> pups at all dose levels. The relative liver weights of weanling F<sub>2</sub> males and females at 20000 ppm were significantly higher (13 to 15% ) than the controls. The mean weights of other organ systems of treated animals did not differ from the controls.

The LOAEL for parental systemic toxicity was 20000 ppm (2509 mg/kg bw), based on decreased body weights (F<sub>1</sub> males), increased relative liver weights in both sexes and bile duct proliferation in F<sub>0</sub> and F<sub>1</sub> parental males. The NOAEL for parental systemic toxicity was 2000 ppm (214.9 mg/kg bw/day in females). There were no effects on fertility or reproductive performance at all dose levels.

The LOAEL for reproductive/developmental toxicity was 20000 ppm (2509 mg/kg bw), based on decreased mean litter weight at day 28 (F<sub>1</sub> and F<sub>2</sub>), reduced body weight development in F<sub>1</sub> and F<sub>2</sub> pups during lactation, increased pup relative liver weights and reduced lactation index in F<sub>1</sub> pups at 20000 ppm. The NOAEL for reproductive/developmental toxicity was 2000 ppm (214.9 mg/kg bw/day in females).

The reproductive study in the rats is classified as acceptable. It satisfies the guideline requirement for a 2-generation reproductive study (OPPTS 870.3800, §83-4); OECD 416 in the rat.

**COMPLIANCE:** Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided

#### **5.5 Additional Information from Literature Sources (if available)**

A literature search was conducted, but no additional toxicity information was found.

## 5.6 Determination of Susceptibility

There was no evidence for increased susceptibility of fetuses to *in utero* exposure of Iprovalicarb in either the rat developmental or rabbit developmental studies. In both studies, the NOAELs for both maternal and developmental toxicity were the highest dose tested, 1000 mg/kg/day (LIMIT DOSE).

Based on the results in the 2-generation reproduction study in rats, a qualitative increased susceptibility of the neonates (as compared with adults) was demonstrated for Iprovalicarb. The parental systemic NOAELs were 146.3/155.3 mg/kg/day for F<sub>0</sub>/F<sub>1</sub> males with the LOAELs being 1514.3/1838.0 mg/kg/day based on decreased body weights and increased liver weights as well as bile duct proliferation; for females, the parental systemic NOAELs were 190.4/239.5 mg/kg/day and the LOAELs were 2074.0/2944.1 mg/kg/day based on increased relative liver weights. Reproductive LOAELs were not attained (> HDT, LIMIT DOSE). In offspring, the NOAELs were 190.4/239.5 mg/kg/day (F<sub>1</sub>/F<sub>2</sub>) and the LOAELs were 2074.0/2944.1 mg/kg/day based on decreased mean litter weight on day 28, reduced body weight during lactation, and increased pup relative liver weights as well as reduced lactation index in F<sub>1</sub>. There was considered to be an increase in sensitivity of the neonates (as compared with adults) because of the lower lactation index (decreased pup survival) and decreased pup body weights.

In addition, the HIARC questioned the lactation index values in the F<sub>2</sub> pups because dose indices, including control, appeared to be "low" (ppm: 0 = 58.2, 100 = 55.9, 2000 = 75.0 and 20000 = 56.4). Historical control lactation indices data (Report Page 523) indicated the following ranges of values for the 14 studies listed (Feb., 1984-Aug., 1992): F<sub>1A</sub> = 99.4-56.8%; F<sub>1B</sub> = 97.3-37%.6; F<sub>2A</sub> = 98.4-35.3%; =F<sub>2B</sub> 97.3-71.5%.

Following the HIARC meeting, HED received additional historical control data from the Registrant on March 5, 2002, which indicated the following: it appears that a lactation index of approx 50-60% is not unusual for the second generation. As indicated above, the historical control data that was submitted with this study had 2 of 14 studies that had lactation indices of approximately 50%. In the recently received historical control data, 3 of 9 studies had lactation indices in the range of 50-60%. Therefore, the 56% lactation index of the F<sub>2</sub> generation seen in the reproduction study is within the historical control range and is not a concern. There is no evidence of treatment-related effect for the lactation index regarding this F<sub>2</sub> generation.

## 5.7 Determination of the Need for Developmental Neurotoxicity Study

### 5.7.1 Evidence that suggests requiring a Developmental Neurotoxicity study:

None

**5.7.2 Evidence that does not support the need for a Developmental Neurotoxicity Study:**

Treatment-related toxicologically significant signs of neurotoxicity were not observed in any of the available studies on Iprovalicarb.

In the developmental toxicity studies on rats and rabbits, treatment-related increased incidences of malformations of nervous system tissues were not observed.

In the developmental toxicity studies on rats and rabbits, treatment-related increased susceptibility of fetuses, as compared with adults, to *in utero* exposure to Iprovalicarb was not demonstrated.

In the 2-generation reproduction study on rats, no increased quantitative sensitivity of the neonates, as compared with adults, was demonstrated for Iprovalicarb.

**6. HAZARD CHARACTERIZATION**

Technical grade Iprovalicarb (also known as TM-210, SZX 0722 and MELODY), a white powder, has no acute oral toxicity in rats (LD<sub>50</sub> in males and females >5000 mg/kg; Toxicity Category IV). As the studies submitted are to support only this import tolerance on grapes and raisins, this acute oral study (98.4% a.i.) and an acute oral in rats at about 50% a.i. (50WG) were the only acute studies submitted to EPA. The 50WG LD<sub>50</sub> was tested only at 500 mg/kg (both sexes) and no clinical signs or mortality were noted ("moderate acute oral toxicity"; Toxicity Category II). Other acute studies with the technical grade, though not received by EPA, were considered to have been Toxicity Category IV (acute dermal rabbit, acute inhalation rat, primary eye irritation rabbit and primary skin irritation rabbit). Dermal sensitization in the guinea pig was negative. The metabolite p-methylphenetylamine had an acute oral LD<sub>50</sub> of 300-500 mg/kg (Toxicity Category II).

In dogs and rats, the liver was the primary target organ with dogs being more sensitive. In a one-year dog study, the NOAEL was about 2.6 mg/kg/day. The following liver-related findings were noted: swelling; enlargement; distinct lobulation; discoloration; increases in absolute and relative weights; increased ALT and ALP values; and hepatocellular hypertrophy as well as periportal fatty change. In 90-day and 28-day dog studies, similar liver-related effects were noted at approximately the same LOAELs. Rat studies of 28 days, 90 days or 2 years duration showed similar liver findings, but at higher LOAELs than for dogs. In mice, no liver-related effects were observed over a 2-year period; but, in a 90-day study, there were increases in liver weights at > limit doses.

In the rat and rabbit developmental studies, there were no apparent maternal or developmental effects at the limit dose. In the 2-generation reproduction study, limit doses resulted in a decrease in body weight gain in males and an increase in liver weights in both sexes. No effects

on reproductive parameters were reported at any dose. Regarding offspring, at the highest dose tested (> limit dose), there was a decrease in mean litter weight on day 28 (F<sub>1</sub> and F<sub>2</sub>), reduced body weight in F<sub>1</sub> and F<sub>2</sub> during lactation and increased pup relative liver weights as well as reduced lactation index in F<sub>1</sub> pups. The lactation index was quite low in all groups (including control) in the F<sub>2</sub> pups.

There were no carcinogenic effects in either a 2-year rat or a 2-year mouse study.

A complete battery of mutagenicity studies was negative.

Following oral administration, there was rapid absorption of radioactivity, wide distribution with minimal tissue residence time, extensive metabolism and rapid elimination which was independent of sex, rate or frequency of dosing. Twelve metabolites were identified with the main metabolite pair being iprovalicarb-carboxylic acid (MO3), >58% of the administered dose. Small amounts of 8 other metabolites were found in urine. The proposed biotransformation pathway was via oxidation of the methyl group on the aromatic ring, leading to carboxylic acid metabolite via hydroxymethyl-derivative.

## **7. DATA GAPS**

At this time, there are no data gaps for this action (import tolerances for grapes and raisins).

## 8. ACUTE TOXICITY

GDLN	Study Type	MRID	Results	Tox Category
81-1, 870.1100	Acute Oral - Rats 98.4%	44865706	M : LD <sub>50</sub> = > 5000 mg/kg F: LD <sub>50</sub> = > 5000 mg/kg No systemic toxicity.	IV
81-1, 870.1100	Acute Oral - Rats 50 WG (about 50% a.i)	44865708	M: LD <sub>50</sub> = 500 mg/kg F: LD <sub>50</sub> = 500 mg/kg 500 mg/kg = only dose No clinical signs or mortality "Moderate Acute Oral Toxicity"	II [II = >50 thru 500, III = >500 thru 5000]
81-1, 870.1100	Acute Oral - Rats <b>METABOLITE:</b> <b>p-Methylphenethylamine</b>	44865707	3/sex/dose, 200 mg/kg; F only at 2000 mg/kg: LD <sub>50</sub> = 300-500 mg/kg <u>signs</u> : incoordination, increased movement, labored breathing, spasmodic state, tonical cramps, rolling over, convulsions, increased salivation and dyspnea; <b>deaths within 15 min. at 2000</b> "High Acute Oral Toxicity"	II
81-2, 870.1200	Acute Dermal - Rabbits	-1	M: LD <sub>50</sub> = > 5000 mg/kg F: LD <sub>50</sub> = > 5000 mg/kg No systemic or dermal toxicity.	IV
81-3, 870.1300	Acute Inhalation - Rats	-1	M: LC <sub>50</sub> = > 4.977 mg/L F: LC <sub>50</sub> = > 4.977 mg/L No systemic or inhalation toxicity.	IV
81-4, 870.2400	Primary Eye Irritation - Rabbits	-1	Not irritating.	IV
81-5, 870.2500	Primary Skin Irritation - Rabbits	-1	500 mg	IV
81-6, 870.2600	Dermal Sensitization - Guinea Pig	-1	Negative	N/A
81-8, 870.6200	Neurotoxicity Screening Battery - Rats	44865731	No systemic or neurotoxic effects at 2000 mg/kg	N/A

(1) = No MRID Numbers were assigned as this information was received from the Registrant.

9. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION FOR  
IPROVALICARB

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary: all Populations	-No toxicological endpoint attributable to a single exposure was identified in the available toxicity studies		
Chronic Dietary	NOAEL = 2.6 UF = 100  RfD = 0.026 mg/kg/day	Effects on liver (increased weight, increased enzyme levels and hepatocellular hyperplasia)	One-Year Dog
Oral Incidental: all Durations	Endpoints were not selected for occupational/residential exposure risk assessments since this petition is for an import tolerance. - -		
Dermal: all Durations			
Inhalation: all Durations			